IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Kim | Group Art Unit: 1648

Serial No. 10/593,413 | Examiner: PENG, Bo

Filed: 9-18-06 | Confirmation No.: 1247

For: ANTI-OBESE IMMUNOGENIC HYBRID POLYPEPTIDES AND ANTI-OBESE VACCINE COMPOSITION COMPRISING THE SAME

Attorney Docket No: 0220.00002

DECLARATION

I, Hyo-Joon Kim, being duly sworn, do hereby state that:

1. I am the inventor of the above-captioned application.

2. I am skilled in the art and have worked extensively in the field of mimetic peptides for the epitope of apolipoprotein B-100 and vaccines related thereto.

3. Claim 11 stands rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Office Action holds that it is not predictable in the art if Apolipoprotein B-100 mini-peptides would prevent or treat obesity in all species, especially in humans.

In response thereto, the specification does show immunogenicity of the compounds of the present invention in rats (see page 18, lines 7-21, Figure 16, and Table 2). Antibody responses to the compounds resulted in the suppression of weight gain in rats. It is well known that experiments are performed in rats and mice that translate directly to humans. Experiments were also performed in dogs with good antibody results and weight gain was also suppressed (see page 20). Therefore, one skilled in the art would expect the compounds to work effectively as a vaccine in humans as well.

Furthermore, WO/2002/20040 (hereinafter Reference 1, enclosed) discloses that in the case that a macromolecule such as an antibody has been bound to apolipoprotein B-100 which exists on the surface of LDL, lipase such as lipoprotein lipase cannot hydrolize triglyceride due to the steric hindrance caused by the macromolecule bound to apolipoprotein B-100, and thus the formation of free fatty acid, a major factor for obesity, can be inhibited by means of the antibody which can bind to apolipoprotein B-100 (see page 2, lines 16-24 and page 8, lines 22-30 of Reference 1).

In addition, Reference 1 discloses the mechanism of vaccine comprising apolipoprotein B-100 to prevent or treat obesity by inhibiting accumulation of lipids like cholesterol of free fatty acid in cells. That is, human antibody induced by mimetic peptide binds to the epitope of apolipoprotein B-100 on the surface of LDL, thereby prohibiting LDL from binding specifically to a LDL receptor exposed on the cell surface (see page 9, lines 8-17 of Reference 1).

As such, since Reference 1, which is the previous invention presented by myself, already discloses the mechanism of vaccine comprising apolipoprotein B-100 in a human, it is not necessary to disclose the mechanism in the present invention. Furthermore, one skilled in the art would easily understand how the hybrid polypeptide of the present invention works as a vaccine in humans, thus undue experimentation is not necessary for one skilled in the art to practice the present invention.

In support thereof, the further included are the following documents to demonstrate how the compounds work as a vaccine in humans and that the vaccine of the present invention provides the same results in humans as shown in animals in the present application.

As seen in Document 1 (Maria Lucia Bonfleur, et al., enclosed) and more specifically on page 24, Table 1 shows that body weight in LDLR knock-out mouse is

reduced, compared to WT. In this regard, antibodies induced by the vaccine of the present invention can prohibit LDL from binding specifically to a LDL receptor and result in preventing or treating obesity.

Furthermore, Document 2 (Gerald F. Watts, et al., enclosed) proves the correlation between the reduction of Apolipoprotein B-100 and the suppression of body weight in humans (see page 284, section 5.2). Thus, Documents 1 and 2 combine to show that the results in animals produced by the vaccine of the present invention are predictable of results in humans.

Reconsideration of the rejection is respectfully requested.

4. Claims 1-11 stand rejected under 35 U.S.C. §103(a) as being unpatentable over WO/2002/20040 to Kim and U.S. Patent No. 6,541,011 to Punnonen.

Kim discloses a mimetic peptide for the epitope of apolipoprotein B-100 which can be used as a vaccine. In this formulation, the active compound can be "mixed or diluted with immune adjuvant" and the immune adjuvant can be proteins containing the epitope of a T cell or T or B cell activators, among other things (p. 6, line 20 – p. 7, line 15). Kim does not disclose an immunogenic hybrid polypeptide, in which the C-terminus of a peptide is fused to the *N*-terminus of a helper T cell epitope as required by the presently amended claims. There is no suggestion or reason in Kim to create such a compound.

While Punnonen discloses an HBV vaccine that can include B or T epitopes from other antigens in the HBsAg sequence, this is a completely different compound from that disclosed in the present invention, and there is no reason to believe that including a T cell epitope in one vaccine means that including one in any vaccine will produce the same results. Furthermore, no evidence is provided in Punnonen that

including a T cell epitope actually works. Thus, there is no reason to combine Kim with Punnonen, especially since Kim shows that the vaccine therein is effective.

The present invention provides improved and unexpected results over the disclosure of Kim because of the inclusion of the T cell epitope in the active compound. "When a T cell epitope was fused to a mimetic peptide of the B cell epitope of apo B-100, $PB1_4$ had improved ability to induce antibody responses and displayed vaccine efficacy for an extended period of time, and so had an excellent anti-obesity effect." Specification, p. 7, lines 24-28. The immunogenicity achieved in the examples is due to the inclusion of the T cell epitope along with the B cell epitope. It was shown on pages 19-20 of the specification that a fusion form of the compound with a T cell epitope has higher immunogenicity than the compound itself, such as that disclosed in Kim.

Please refer to page 22, line 23 to page 23, line 21 of the present application, which describes investigations on the effect of the orientation of the B cell epitope and the helper T cell epitope on the induction of immune response. A T cell epitope was fused at the N-terminus of an apo-B mimetic peptide, and compared that orientation to the orientation as recited in the invention described by the claims of the present application, namely, a T cell epitope fused at the C-terminus of an apo-B mimetic peptide. It was determined that the polypeptide prepared by linking a C-terminus of the apo-B mimetic peptide to a T cell epitope exhibited a 50-60% enhanced ability to induce antibody response (see Figure 16), and to suppress body weigh gain (see Table 2), as compared to the polypeptide prepared by linking an N-terminus of the apo-B mimetic peptide to a T cell epitope. Thus, the results indicate that a polypeptide prepared by linking a C-terminus of the apo-B mimetic peptide to a T cell epitope as recited in the claims of the present invention has much stronger immunogenicity and anti-obesity effects. However, neither Kim nor Punnonen

disclose or suggest these unexpected results, and it would not be obvious for one skilled in the art to make the present invention.

The undersigned declares further all statements made herein of his knowledge are true and that all statements made upon information and belief are believed to be true, and further that the statements were made with the knowledge that willful and false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Jan. 12th, 2010

Hyo-Joon Kim